REMARKS

I. INTRODUCTION

Applicants respectfully acknowledge the allowance of claim 35. Claims 16-20, 22-26 and 33-35 remain in the application. Re-consideration of the application in view of the following remarks is requested.

II. EXAMINER INTERVIEW SUMMARY

Record is made of telephone interviews on December 19, 2003 and January 7, 2004 between Applicants' attorney William Wood and Examiner Billy D. Chism in connection with the present patent application. Applicants' Attorney wishes to thank Examiner Chism for his helpful comments.

III. NON ART REJECTION

Claims 16, 20, 22, 26, and 33-34 were rejected under 35 U.S.C. §112, first paragraph. In this rejection, the Examiner asserts that the specification, while being enabling for methods of making compositions comprising human insulin/LISPRO heterodimeric complexes, does not reasonably provide enablement for methods of making any and/or all compositions comprising a heterodimeric complex of human insulin and any insulin variant. In particular, the Examiner asserts that it would require undue experimentation to practice an invention encompassing a genus of heterodimeric complexes because "neither the assay nor the disclosure gives method steps on how to predictably select complementary first and second insulin species to yield adequate bioactive compounds" and "the undue experimentation [results from] the fact that there is no way of knowing if the selected species will work as claimed in a stabilized heterodimeric complex" (see, e.g., the first paragraph on page 3 of the Office Action dated October 21, 2003, Paper #10).

The arguments presented below respond to the Examiner's rejections. The first section demonstrates how Applicants' disclosure satisfies the requirements of 35 U.S.C. section 112, first paragraph by providing guidance on how to make and use the insulin heterodimers commensurate with the scope the claims. The second section explains why the Patent Office's interpretation of the requirements of 35 U.S.C. 112 is contrary to case law.

A. APPLICANTS' DISCLOSURE IS COMMENSURATE WITH THE SCOPE OF PROTECTION DEFINED BY THE CLAIMS

Applicants' claims are narrowly drawn to heterodimeric complexes of insulin, a well known polypeptide. In this context, Applicants' specification discloses an exemplary embodiment of the claimed invention as well as providing detailed teachings of how to characterize any heterodimeric insulin formulation encompassed by the claims. In particular, in order to determine whether any combination of any two insulin species can be used to generate the stabilized insulin heterodimers of the invention, an artisan need only prepare 3 test samples consisting of: (1) the first insulin species alone, (2) the second insulin species alone and (3) a combination of the first insulin species and the second insulin species; and then test the stability of the 3 test samples in an assay such as the Thioflavin-T assays disclosed in Example 2. Moreover, Applicants' working example of human insulin/LISPRO heterodimeric complexes provides a positive control to confirm the fidelity of such assays. This disclosure therefore allows an artisan to readily assess the ability of any one insulin species to form a stable heterodimer with another insulin species (e.g. by the preparation and testing of the three insulin species formulations as discussed above). While the outcome of a given assay may be unpredictable, the amount of experimentation necessary to determine the result (i.e. prepare and analyze 3 test samples) is routine.

Applicants further note that both the example provided in the specification as well as reports in the technical literature provide evidence that one could reasonably expect to obtain the stabilized heterodimers recited in the claims. Specifically, the identification of heterodimeric complexes of homologous molecules having a greater stability than homodimers formed by the molecules is consistent with a number of reports in the technical literature. For example, Gimona et al., P.N.A.S. 92: pp: 9776-9780 (1995) teach that the heterodimeric complex formed by two homologous tropomyosin polypeptides (designated "α" and "β"), is thermodynamically more stable than either the α/α homodimer or the β/β homodimer complexes that are typically formed from the individual polypeptides. In addition, Müller et al., JBC 278(20): pp: 18330-18335 (2003) teach that the heterodimeric complex formed by two homologous platelet derived growth factor ("PDGF") polypeptides (designated "A" and "B"), forms three times more rapidly than the PDGF-AA homodimer or the PDGF-BB homodimer complexes that are typically formed from the individual polypeptides. As these PDGF-AB polypeptide complexes are observed to be more stable that the

individual polypeptides in solution, this rapid formation of the heterodimeric complex serves to stabilize the polypeptide subunits in solution to a greater degree than the respective homodimeric complexes. Applicants' disclosure relating to insulin heterodimers is therefore consistent with art pertaining to polypeptides having analogous properties (e.g. the ability to form both homodimers and heterodimers). The Gimona et al. and Müller et al. references are attached herein as Appendix A.

In view of the disclosure in the specification and the above noted technical articles, Applicants traverse the outstanding enablement rejection. While the Examiner is correct in noting that experimentation is needed to practice the invention commensurate in scope with the instant claims, courts recognize the propriety of reasonable experimentation that used to verify a characteristic of an invention. Specifically, courts find that the routine experimentation undertaken to ascertain various unpredictable factors is not fatal to a finding of enablement.[1] For example, court decisions explicitly state that the Section 112 enablement requirement implicitly tolerates a disclosure requiring "experimentation" to make or use the claimed invention so long as the experimentation is not "undue" or "unreasonable."[2]

In an enablement rejection based on undue experimentation, the focus is not on the need for experimentation per se, but rather undue experimentation. In this context, all that is required is a disclosure, which allows one to make and use the invention as broadly as it is claimed. In the instant application, Applicants claim methods for forming stabilized insulin heterodimers, and teach that the stability of such heterodimers may be readily determined via assays such as the Thioflavin-T assays disclosed in Example 2. While a Thioflavin-T assay may require that the skilled artisan spend a number of hours of experimentation to determine the stability of a heterodimeric complex, this amount of experimentation is by no means undue. Because a skilled artisan can therefore perform this routine analysis on the claimed variants without an inventive contribution or undue experimentation, Applicants' disclosure is commensurate with the scope of protection defined by the claims.

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1 See e.g. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

2 See e.g., *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991), *cert. denied*, 112 S. Ct. 169 (1991), ("That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive."); *In re Wands*, 858 F.2d 731, 736-37, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) ("Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is "undue," not "experimentation." "; *Hybritech, Inc. v. Monoclonal Antibodies*, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987) (enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive").

Consequently, Applicants' disclosure satisfies the requirements of 35 U.S.C. section 112, first paragraph.

B. THE PATENT OFFICE'S INTERPRETATION OF THE REQUIREMENTS OF 35 U.S.C. SECTION 112, IS CONTRARY TO CASE LAW.

In the instant enablement rejection, the Examiner asserts that because one cannot predict which insulin species will yield the stabilized heterodimers recited in the claims, this property must be characterized and that the amount of experimentation needed to characterize this property is undue. In support of this rejection the Examiner states "neither the assay nor the disclosure gives method steps on how to predictably select first and second insulin species to yield adequate bioactive compounds" (see, e.g., the first paragraph on page 3 of the Office Action dated October 21, 2003, Paper #10).

Applicants respectfully traverse this rejection because a finding of non-enablement predicated on the observation that species generated by Applicants' claims have an unpredictable characteristic is contrary to case law. This is shown, for example, by the holding of *In re Angstadt*, a case which discussed the enablement of organometallic complexes having an unpredictable catalytic activity. *In re Angstadt and Griffin*, 190 USPQ 215, 218 (CCPA 1976). In *In re Angstadt*, the court held that the disclosure enabled the invention even when it was not possible to predict the activity of a compound encompassed by the claims (and one must therefore characterize this property after each compound is made). **In discussing the reasoning for their holding, the court in *In re Angstadt* explained that if 35 U.S.C. section 112 was interpreted to require that a disclosure must provide "guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction, whether the claimed product will be obtained" (e.g. the "adequate bioactive compounds" cited by the Examiner in the instant rejection), then "all 'experimentation' is 'undue' since the term 'experimentation' implies that the success of the particular activity is uncertain" (*In re Angstadt* at 219).** The court went on to explain that such a predictability requirement is contrary to the Patent Act and that to require disclosures in patent applications to transcend the level of knowledge of those skilled in the art will stifle the disclosures of inventions in fields man understands imperfectly. *Id.*

As illustrated above, the court in *In re Angstadt* held that when an unpredictable characteristic of an invention can be determined by routine screening, the need for such screening did not preclude enablement. The court in *In re Wands 858 F.2d 731 (Fed. Cir. 1988),* reiterated this holding when it found that the amount of experimentation required to determine the affinity of antibody species encompassed by Wands' claims was not undue, even when this characteristic could not be predicted. Consequently, the Examiner's enablement rejection, which is predicated on the observation that the heterodimeric insulin complexes recited in Applicants' claims have a similarly unpredictable characteristic, is contrary to case law. Illustrating this, Applicants note that if the Examiner's arguments (i.e. that the experimentation necessary to evaluate an unpredictable interaction between two proteins is undue) were applied to the facts at issue in *In re Wands,* Wands' claimed "monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9 m^{-1}"[3] would not be enabled because the skilled artisan cannot predict the affinity an antibody has for its antigen (e.g. HBsAg) and consequently, must perform experiments to determine this property. The Federal Circuit in *In re Wands* however, found the wide spectrum of antibodies encompassed by this claim to be enabled, holding that the amount of experimentation necessary to characterize an unpredictable interaction between two proteins (e.g. the interaction between Wands' antibody and HBsAg) is not undue. Consequently, the amount of experimentation necessary to practice the Applicants' invention is also not undue.

In summary, Applicants' disclosure places the public in possession of an invention based upon the discovery that insulin/insulin variant heterodimers can exhibit a greater stability than insulin homodimers. The instant claims are narrowly drawn to such insulin heterodimers and Applicant concurrently discloses those protocols that allow artisans to characterize any insulin/insulin variant heterodimeric formulation via routine experimentation. The Examiner is correct in noting that some experimentation is required to characterize the stability of insulin heterodimeric complexes encompassed by the claims. However, the facts and holdings in *In re Angstadt* and *In re Wands* confirm that such uncertainty cannot be used to support a rejection under 35 U.S.C. section 112, first paragraph when this property can be readily characterized by routine protocols. The withdrawal of this rejection is therefore requested.

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3 *In re Wands,* 858 F.2d at 733.

IV. CLAIM OBJECTIONS

At item 3 in the outstanding office action, claims 17-19 and 23-25 were objected to because they "are drawn to rejected claims". As noted above, the rejection of these claims should be withdrawn because it is contrary to case law. For this reason, Applicants similarly request the withdrawal of the outstanding objection to claims 17-19 and 23-25.

V. CONCLUSION

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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